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## Risperidone—A New Antipsychotic Agent

RISPERIDONE is the first antipsychotic agent designed to antagonize both dopamine and serotonin receptors as does clozapine. Unlike clozapine, it has little effect on cholinergic and  $\beta$ -adrenergic receptors but does affect  $\alpha_2$ -adrenergic and histamine  $H_1$  receptors.

In a series of controlled studies, risperidone has been shown to be an active antipsychotic agent in doses ranging from 4 to 16 mg. Dosages greater than 6 mg have not shown greater activity, but have more side effects, including extrapyramidal signs. The use of a dose of 6 mg was shown to be superior to both a placebo and 20 mg of haloperidol and with no difference in extrapyramidal effects compared with the placebo. Thus, at this dosage, a beneficial effect was seen in both "positive" (such as delusions and hallucinations) and "negative" (such as emotional withdrawal and blunted affect) symptoms with a minimum of extrapyramidal signs. This led to the suggestion of the rapid titration of this dosage for everyone, but clinical experience has shown this to be a mistake. First (and apart from its cost), not all patients require 6 mg. Second, although there was no group difference between the use of 6 mg and a placebo, extrapyramidal signs do develop in some persons at this dosage, with dystonic reactions reported at dosages as low as 2 mg. It appears now that risperidone is probably twice as potent as haloperidol; therefore, maintenance dosages will generally range from 1 mg upwards, with individual dose titration as necessary. Many patients do well at 3 or 4 mg per day, and the use of 4 mg has been shown to be therapeutic in a European controlled trial. For older patients, even smaller dosages have been shown to be effective. Specific controlled studies in these patients have not yet been reported in the literature, but clinical reports of the use of doses lower than 1 mg being effective have led the manufacturer to try producing tablets smaller than 1 mg and a liquid preparation as well.

Risperidone has a half-life of 3 to 20 hours and is extensively metabolized to an active agent, 9-hydroxyrisperidone, which has a half-life of 21 to 30 hours. This metabolism takes place in the liver through the cytochrome P-450 IID6 isoenzyme system. This enzyme system is responsible for the metabolism of many neuroleptic and antidepressant agents, creating the possibility of important drug interactions. Isomorphism of this enzyme activity may explain the individual differences in metabolism. The majority of the drug's activity derives

from the 9-hydroxy metabolite; yet, despite the long half-life of this metabolite, twice-a-day dosing is recommended by the manufacturer. This is apparently a Food and Drug Administration requirement despite the lack of any studies of once-a-day dosing. Drugs such as thioridazine, haloperidol, and loxapine are frequently used once a day at bedtime in routine clinical practice despite the lack of studies of once-a-day dosage. For the treatment of psychotic states, a starting dose of 1 mg twice a day should be used and the dosage increased slowly as the clinical state dictates, similar to the use of other antipsychotic agents. Converting from a typical neuroleptic to risperidone should not be done abruptly. It is also important not to discontinue anticholinergic drugs abruptly because this may lead to a worsening of extrapyramidal signs. If a patient is taking anticholinergic drugs, these should be continued and later withdrawn slowly after the transition to risperidone has taken place. Side effects with the use of risperidone include dizziness, sleepiness, and nausea, which, like extrapyramidal effects, are probably dose-related. Tachycardia and weight gain have also been reported.

Risperidone is expensive, costing as much as \$2,000 per year per patient, but it offers an advantage over conventional neuroleptic agents in some patients, with about a 15% better response rate. It represents a distinct advance in therapeutics, particularly because it does not require blood monitoring, as does the use of clozapine. The exact place of risperidone in therapeutics is still to be determined. Many psychopharmacologists think that it should be a treatment of first choice in schizophrenia. Others suggest that patients should have an adequate trial of at least one typical neuroleptic agent, such as chlorpromazine or haloperidol, and if nonresponsive to this, then risperidone would be the next choice. The place of risperidone in the treatment of older patients or in affective disorders and other conditions where antipsychotic agents are used remains to be determined.

GEORGE M. SIMPSON, MD  
Los Angeles, California

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## Managing Agitated Patients in a General Hospital

AN AGITATED PATIENT in a general hospital setting is disruptive, dangerous, and usually in delirium. Agitated patients cause delays in patient recovery, increase patient and hospital costs, heighten family and staff anxiety, and can lead to patient and staff injury. Severely agitated patients show excessive physical activity and present a serious risk to themselves. Delirium is the most frequent cause of severe agitation in a general hospital, though mania, psychosis, dementia, and severe anxiety or depression can sometimes present with substantial agitation.

Delirium is a reversible impairment of cognition characterized by disorientation, impaired short-term memory, short attention span, altered perceptions of the environment, abnormal thought processes, inappropriate behavior, fluctuating levels of consciousness, and a worsening of symptoms at night. The last two symptoms are virtually diagnostic of delirium. Several factors usually contribute to delirium in patients, and a multifactorial cause should always be considered. Patients with dementia brain injury and older persons are particularly vulnerable to delirium.

The first priority in managing agitation due to delirium is to assess and treat the underlying cause. The immediate management of a patient's dangerous behavior usually requires additional intervention, however. Physical and chemical restraints can be effective in managing severe agitation and lowering the risk of injury to patients and staff. Mildly to moderately agitated patients who are responsive to verbal intervention can usually be managed with a multidisciplinary treatment plan that emphasizes physical and emotional supportive care, structured routines and activities, and the manipulation of environmental stimuli to help orient the patient and improve his or her coping mechanisms.

The cornerstone of chemical restraint for agitated patients is a high-potency neuroleptic agent. Haloperidol is most frequently used because of its ease of administration and titration and its reduced anticholinergic effect compared with other neuroleptics. The starting dose for acutely agitated patients can be from 1 to 10 mg, given by intravenous push, depending on the patient's age, size, and degree of agitation. Older patients should be started on lower doses of 1 to 3 mg. If the patient remains agitated, the starting dose should be doubled and readministered every 15 to 20 minutes until agitation is controlled. The patient should be closely monitored for adverse medication effects, including extrapyramidal symptoms, acute dystonia, akathisia, and the development of the neuroleptic malignant syndrome. Akathisia, a feeling of motor restlessness, is often mistaken for increased agitation. Most extrapyramidal symptoms respond to the use of antiparkinsonian agents, such as diphenhydramine, or to benzodiazepines.

Several other pharmacologic agents are used to control agitation. The use of benzodiazepines in combination with haloperidol is frequently helpful. Diazepam and lorazepam are easily administered and have a rapid onset of action. Lorazepam is used in patients with compromised liver function. Patients who are agitated during alcohol or sedative withdrawal can be managed with benzodiazepines alone. Aggressive management is recommended to prevent delirium tremens. Narcotic withdrawal and associated agitation should be managed with opioids. Patients who have been taking narcotics or benzodiazepines long term should be carefully tapered to prevent the development of agitation. Other psychotropic agents often used to control agitation and impulsivity include divalproex sodium, carbamazepine, propranolol, and buspirone.

Intensive care units are the most frequent setting for the occurrence of severe agitation because of the multiple stressors contributing to delirium and anxiety in patients. These include painful procedures or activities, environmental stimulation from constant noise and light, physical restraints, mechanical ventilation, and an unfamiliar environment. Frequently agitation occurs at the time a patient awakens from anesthetics, narcotics, and sedatives given at the time of admission or a surgical procedure. Inadequate pain control is a frequent contributor to agitation and must be carefully evaluated. A comprehensive treatment plan with good supportive care can minimize the need for physical and chemical restraints.

MARK SERVIS, MD  
Sacramento, California

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### Diagnostic and Therapeutic Advances in Treatment-Resistant Mood Disorders

TREATMENT RESISTANCE poses a serious clinical dilemma for psychiatrists and may result in prolonged and serious consequences for patients, including death. When there is minimal response to treatment with antidepressant agents, psychotherapy, and supportive interventions and despite a trial of sufficient length, a systematic analysis becomes imperative to break through the stalemate.

Nearly a third of depressed patients (30%) fail to respond to conventional therapy, and as many as 60% have insufficient improvement of clinical indices at recovery. Obvious initial considerations involve a reassessment of the diagnosis (unipolar, bipolar, atypical, rapid cycling, seasonal), medication dosage, patient compliance with treatment, and the presence of comorbid psychiatric and medical disorders (including substance abuse, cognitive disorders, and endocrine and oncologic disorders).

Although brain imaging procedures are not definitive diagnostic or predictive tools for treatment resistance, they have great promise for understanding structural and neurochemical abnormalities that may define a treatment plan for specific patients. For example, one study using hexamethylpropylene amine oxime and single-photon-emitted computed tomography has implied that the limbic system plays an important role in mediating treatment refractoriness.

Gender, genetic, and age characteristics may contribute to mood disorder subtypes (psychosis, catatonia, pseudodementia, and severe vegetative signs) requiring specific intervention. Special pharmacokinetic issues such as medication absorption, interaction, and plasma drug concentration should be considered because there